

nervous system function that are distinct and readily identifiable. In addition, the similar findings observed in studies using different routes of nicotine administration are consistent with the hypothesis that the tobacco vehicle is not necessary to produce nicotine-associated changes of mood and feeling. The next Section examines data from analogous studies in which humans served as research subjects.

Psychoactivity of Nicotine

The animal research described above indicates that nicotine's psychoactivity is a result of basic biological actions. Human research on nicotine corroborates the validity of the animal research. Results from studies of the interoceptive effects of nicotine in humans are analogous to those obtained in animal studies described above.

One of the first human studies that used drug discrimination procedures, as had been developed with animal subjects, was a study of nicotine discrimination. The study involved the systematic manipulation of nicotine dose levels with research cigarettes which varied primarily in the amount of nicotine delivered (Kallman et al. 1982). This study demonstrated that nicotine, as delivered by the inhalation of tobacco smoke, produces discriminative stimulus effects. The degree and rate of acquisition of the discrimination appeared to be dose dependent. The ability of the subjects to make the discriminations did not appear to be related to either autonomic (e.g., heart rate) effects of nicotine or to nicotine's effects on other self-reported measures (e.g., taste of the cigarette).

The data from Kallman and associates (1982) are consistent with those of several other studies which have found that human volunteers can differentiate among cigarettes which vary mainly in the amount of nicotine which they deliver (Goldfarb, Jarvik, Glick 1970; Goldfarb et al. 1976; Herskovic, Rose, Jarvik 1986; Rose 1984; Griffiths, Bigelow, Henningfield 1980; Henningfield, Miyasato, Johnson, Jasinski 1985). Furthermore, the conclusion that centrally mediated effects of nicotine are important in such responsivity is supported by findings that pretreatment with mecamylamine reduced responsivity to nicotine dose levels of the cigarette (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau et al. 1987). The study by Stolerman and associates (1973) also showed that such antagonism of nicotine's effects was not obtained when peripherally acting pentolinium was given.

Other research has confirmed that the tobacco vehicle is not necessary to enable the interoceptive effects of nicotine. Several studies involving i.v. administration of nicotine in human subjects have found that humans readily differentiate among nicotine dose levels given intravenously. In the earliest of these studies, i.v. injections of nicotine were given to 35 volunteers, most of whom were cigarette smokers (Johnston 1942). The conclusions of Johnston

TABLE 3.—Summary of early observations regarding psychoactivity of intravenously delivered nicotine in humans

1.	"Psychic" effects are directly related to nicotine dose; nonsmokers are much more sensitive to toxic symptoms (e.g., nausea) than smokers
2.	Effect of nicotine is "specific and readily distinguished from that of cocaine or codeine"
3.	Nicotine injections are "pleasant" to smokers, and are preferred by some over cigarette smoking
4.	Orally given nicotine (dissolved in water) also had "psychic" action, but appeared much less potent than intravenously administered nicotine; delayed onset of effect
5.	~ 1-3 mg doses appeared tolerable and equivalent to smoking single cigarette; ~ 0.11 mg doses appeared to produce "subjective sensation" equivalent to one "deep" cigarette smoke inhalation

*More recent research indicates that higher dose levels of nicotine can produce cocaine-like effects (Henningfield, Miyasato, Jasinski 1985).

SOURCE: Johnston (1942).

that are especially relevant to characterization of the psychoactivity of nicotine are shown in Table 3.

Johnston's findings (Table 3) have been generally confirmed. Jones, Farrell, and Herning (1978) and Rosenberg and colleagues (1980) also found that human volunteers could differentiate i.v. nicotine at dose levels similar to those obtained by smoking cigarettes. In another study which extended the findings of Johnston (1942), both i.v. nicotine and nicotine inhaled from research cigarettes across a range of doses were administered to human volunteers with histories of using a variety of dependence-producing drugs (Henningfield, Miyasato, Jasinski 1985). Subjects clearly distinguished nicotine from a placebo, and the dose strength estimates were directly related to the nicotine dose level. A subsequent study showed that the immediate subjective effects of nicotine were diminished by pretreatment of subjects with mecamylamine (Henningfield et al. 1983).

In a study by Henningfield, Miyasato, Jasinski (1985), measures used to qualitatively describe the nature of the drug stimulus indicated that nicotine met criteria as a euphoriant. At higher doses nicotine was sometimes identified as a stimulant (cocaine or amphetamine); it elevated scores on the Morphine Benzedrine Group ("Euphoria" or "MBG") scale of the Addiction Research Center Inventory (ARCI) (Haertzen and Hickey 1987); and it produced dose-related increases in scores on a drug-liking scale. The high-dose cocaine/amphetamine identifications found in the study by Henningfield, Miyasato, and Jasinski (1985) were not observed by

Johnston, but such similarities between nicotine and cocaine may only be clearly identifiable by subjects experienced with both cocaine and nicotine.

Nicotine given in the polacrilex gum form has been evaluated with similar measures as described above. These studies involved giving various combinations of 2-mg- and 4-mg-nicotine pieces of polacrilex gum and placebo to cigarette smokers. Human volunteers were given the polacrilex gum to chew in doses ranging from 0 to 4 mg in one study (Nemeth-Coslett and Henningfield 1986) and 0 to 8 mg in another study (Nemeth-Coslett et al. 1987). Both studies showed that subject ratings of several effects (including "dose strength") were directly related to the total dose of nicotine that was given. In addition, similarity of the stimulus effects to those produced by cigarettes was a direct function of dose level. In these studies "liking" or "positive" effect scores were inversely related to dose level, suggesting that this nicotine delivery system has low potential for causing dependence when compared with that of cigarettes (Chapter VII). The role of centrally mediated nicotinic actions in the ability of humans to differentiate among polacrilex gum-delivered nicotine doses was confirmed in a study by Pickworth, Herning, and Henningfield (in press). These researchers found that mecamylamine pretreatment of human volunteers reduced both the EEG and subjective effects of nicotine polacrilex gum administration.

Like many other psychoactive drugs (Chapter V), nicotine can also produce unpleasant or dysphoric subjective effects that are related to the dose given and the route of administration. Such effects can be quantified by a psychological scale of the ARCI that is sometimes referred to as the "dysphoria" scale (Jasinski, Johnson, Henningfield 1984) or the "LSD" scale because it was constructed from items found to be elevated when lysergic acid diethylamide (LSD) was given to volunteers (Haertzen 1966, 1974).

In one study, Henningfield, Miyasato, and Jasinski (1985) found that both inhaled (research cigarette smoke) and i.v. nicotine produced dose-related increases in LSD scale scores. In two other studies, nicotine polacrilex gum was tested (Nemeth-Coslett and Henningfield 1986; Nemeth-Coslett et al. 1987). LSD scale scores were at least slightly increased in both studies and were significantly increased in the study by Nemeth-Coslett and Henningfield (1986). These results with nicotine polacrilex gum, combined with no increases in MBG scale scores, are consistent with the observations described earlier suggesting a low overall dependence potential for this formulation.

Sensory Effects of Nicotine

As discussed earlier in this Chapter, nonnicotine constituents of tobacco smoke can produce functional sensory effects. Nicotine, too,

can produce peripherally mediated sensory effects which could contribute to the taste of the cigarette. Although not generally termed "psychoactive" drug effects, such effects could contribute to the control over behavior as they provide discrete cues which may be associated with centrally mediated nicotinic effects. For example, nicotine has a bitter taste, elicits burning sensations when placed on the tongue, and is irritating to the oral and respiratory mucosa (Windholz et al. 1976). Increasing the nicotine delivery of cigarettes while holding tar delivery constant leads to an increase in perceived strength and harshness. The possible effects of nicotine in the upper respiratory tract on subject ratings cannot be excluded in these studies. Nicotine also stimulates mechanoreceptors sensitive to pressure and stretch (Taylor 1985b), and this local action of nicotine may also contribute to the sensory characteristics of inhaled cigarette smoke.

Hexamethonium (the nicotine receptor antagonist that only acts peripherally) has been shown to block cigarette smoke-induced edema in the tracheobronchial mucosa of rats (Lundberg, Saria, Martling 1982). Another study showed that mecamylamine produced dose-related decreases in harshness ratings of individual puffs of cigarette smoke (Rose, Sampson, Henningfield 1985). In this study, subjects were asked to rate their preference at different nicotine concentrations of the smoke: mecamylamine pretreatment shifted preferences to higher smoke concentrations for individual puffs.

Another method of producing at least some of the nicotine-related sensations of cigarette smoke is to present nicotine in vapor or aerosol form without any components of tar. Nicotine vapor is likely to be deposited mainly in the mouth and pharynx (Russell 1986); thus it would be difficult to administer a pharmacologically effective dose of nicotine without producing excessive local irritation and bad taste. However, a low dose of nicotine delivered in this fashion might simulate the sensory effects of smoking, even if the pharmacologic effects are minimal. A low-dose nicotine aerosol delivering droplets 1 to 5 μm in size would be expected to provide respiratory sensations even more similar to cigarette smoking, as particles of this size would impact mainly in the tracheobronchial region.

Three studies have evaluated the effects of a commercially marketed nicotine vapor delivery system in human subjects. The delivery system was a version of that originally described by Jacobson, Jacobson, and Ray (1979); it was marketed as a "tobacco product" through February 1987, when the Food and Drug Administration (FDA) required verification of "safety and efficacy" for continued marketing as a "nicotine delivery system" (see Chapter VII). It consisted of a cigarette-size plastic tube with a nicotine-containing polymer in the end distal from the user's mouth. It was used by sucking air through the tube and inhaling in a manner

similar to that when smoking cigarettes. When the system was used in this fashion, two studies found that plasma nicotine levels were not significantly elevated (Sepkovic et al. 1986; Henningfield 1986b). A third study found significant elevations in plasma nicotine following use of the nicotine tube (Russell et al. 1987). However, in the latter study subjects used what may be described as a heroic puffing procedure: they were instructed to puff 1 nicotine tube 10 times, at intervals of 40 sec; after a 4-min pause, subjects then "puffed and inhaled as hard and as frequently as possible, continuously for the next 20 min, with changes every 5 min to fresh cigarette [nicotine tube]." Symptoms typical of those associated with higher levels of nicotine administration were observed, i.e., dizziness, lightheadedness, and in a few subjects, nausea (Russell et al. 1987).

In another study of the nicotine vapor inhaler, four tubes in which none, one, two, or four contained nicotine (the others being denicotinized) were simultaneously puffed on by volunteers through a specially designed cigarette holder (Henningfield 1986b, 1987a). In this study, despite the fact that measurable changes in plasma nicotine levels did not occur, several responses often associated with nicotine delivery were observed: (1) subject ratings of "harshness" were directly related to dose (number of nicotine-containing tubes); (2) post-puffing increases in heart rate occurred as a function of dose; (3) subjective effects were directly related to dose; and (4) desire to smoke tobacco cigarettes was inversely related to nicotine dose level. Taken together, these results show that even with negligible systemic levels, nicotine can induce feelings of satisfaction and can reduce urges to smoke when it produces tobacco-like sensations of throat burn and harshness (Chapter VII).

Some of the short-term satisfaction derived from inhaling nicotine may explain the apparent short-term efficacy of the vapor inhaler in reducing desire to smoke despite negligible plasma nicotine levels. This is in contrast to findings obtained when nicotine is given either intravenously or in the polacrilex gum (Henningfield, Miyasato, Jasinski 1983; Nemeth-Coslett et al. 1987). Whether the effects of the nicotine vapor inhaler are conditioned responses, peripheral nicotinic actions, or both, it remains to be determined if such effects would provide long-term efficacy as tobacco replacement in the nicotine-dependent tobacco user (Chapter VII). Such effects may not be satisfactory for long-term treatment (i.e., they may not satisfactorily alleviate tobacco withdrawal), although they may prove important in providing sources of pleasure and reduction of urges in people trying to quit smoking (Henningfield 1987b).

State-Dependent Learning

The potential of nicotine to induce state-dependent learning effects as well as how such effects are studied are discussed in

Chapter VI. In the present Section, findings are summarized in so far as they are relevant to assessing the dependence potential of nicotine. In brief, state-dependent learning refers to the phenomenon whereby behavior learned in one set of cues or stimulus conditions (context) is most reliably performed when subsequently attempted in the same context and/or is adversely affected when attempted in a novel context (Chapter VI). Psychoactive drugs can produce state-dependent learning effects, apparently by providing a recognizable context based on the interoceptive stimulus cues provided by the drug (see also Chapter V). Several studies have shown that nicotine exposure can lead to state-dependent learning effects. For example, a series of studies conducted by Andersson and colleagues (Andersson 1975; Andersson and Hockey 1977; Andersson and Post 1974) and by others (Peters and McGee 1982; Warburton et al. 1986) showed that nicotine exposure in the form of tobacco smoke could induce state-dependent learning effects in humans. In a study by Lowe (1985), nicotine's part in the state complex produced by alcohol and nicotine together was also evaluated.

There are two implications of the above findings regarding the dependence potential of nicotine. The first is that state-dependent learning could contribute to the dependence potential of cigarettes, in that optimal cognitive/behavioral performance may come to depend upon the continued self-administration of tobacco. These actions might also contribute to the strength of the reinforcing effects of nicotine by producing effects on learning and/or performance (see also Chapter VI).

Nicotine as a Positive Reinforcer

The primary biobehavioral mechanism by which dependence-producing drugs maintain drug seeking is by functioning as positive reinforcers (Thompson and Unna 1977; Thompson and Schuster 1968). That is, drugs can serve as stimuli that strengthen behavior leading to their own presentation (Skinner 1953; Thompson and Schuster 1968). As discussed in Chapter V, studies in the 1960s used the drug self-administration techniques developed to study morphine and other dependence-producing drugs in animals (Weeks 1962; Thompson and Schuster 1964; Chapter V). In the first such study with nicotine, Deneau and Inoki (1967) found that monkeys would also self-administer nicotine intravenously. However, some investigators considered these findings equivocal (Russell 1979; Griffiths, Brady, Bradford 1979). In 1981, Goldberg, Spealman, and Goldberg showed conclusively that nicotine itself could function as an efficacious positive reinforcer for animals, although the range of conditions under which it was effective was somewhat more limited than for drugs such as cocaine and amphetamine. Analogous studies with humans in the 1980s (e.g., Henningfield, Miyasato, Jasinski

1983) demonstrated that intravenously administered nicotine is a reinforcer. The results leading to the foregoing conclusions are summarized in the present Section.

Animal Studies of Nicotine as a Reinforcer

Whether a drug functions as a reinforcer can depend critically on the dose of drug, the previous exposure of the subject to that or other drugs, the behavioral history of the subject, and perhaps most importantly, the immediate contingencies relating responses and subsequent injections of drug (contingencies are often referred to as schedules of reinforcement) (Barrett and Witkin 1986; Chapter V). Nicotine differs from some dependence-producing drugs (e.g., cocaine) (Griffiths, Brady, Bradford 1979) in that for animals, the conditions under which it maintains high rates of self-administration behavior appear to be more limited; however, there are other dependence-producing drugs which also serve as reinforcers under a fairly limited range of conditions (e.g., alcohol) (Mello 1973; Meisch 1977).

Table 4 (modified from Henningfield and Goldberg 1983b) is a summary of the early studies that found i.v. nicotine injection to be ineffective or marginally effective as a reinforcer as well as more recent studies that conclusively demonstrated the capacity of nicotine to function as a positive reinforcer. The studies listed in this Table employed a variety of species (ranging from rats to human volunteers), different types and parameters of drug injection schedules, a variety of training histories, and a wide range of nicotine doses. Much of the research has been reviewed in greater detail elsewhere (Goldberg and Henningfield, 1988; Swedberg, Henningfield, Goldberg, in press). The present Section only reviews some of the more recent studies that have experimentally evaluated nicotine's reinforcing effects.

Until 1981, most experiments of nicotine self-administration involved continuous reinforcement schedules in which each response by an individual subject resulted in the i.v. injection of nicotine (Table 4). Under these continuous reinforcement schedules, (1) rates of responding were very low, ranging from about 0.008 to 0.0005 responses/sec in different studies; (2) changes in nicotine dose produced only small and inconsistent changes in rates of responding; (3) the differences in rates of responding maintained by nicotine compared with saline were generally small; and (4) marked intersubject differences in self-administration of nicotine were often reported. In one series of studies (Lang et al. 1977; Singer, Simpson, Lang 1978; Latiff, Smith, Lang 1980; Smith and Lang 1980) a concurrent schedule of periodic deliveries of food pellets to food-deprived rats was found to increase rates of nicotine self-administration responding (Chapter V). The concurrent food reinforcement schedule ap-

TABLE 4.—Summary of reports in which nicotine was available under intravenous drug self-administration (S-A) procedures

Study	Species	Reinforcement schedule	Main findings	Comments
Deneau and Inoki (1967)	Rhesus monkey	FR 1; several nicotine doses tested	Two monkeys initiated S-A; others required priming procedure	Currently accepted reinforcing efficacy assessment criteria not achieved
Clark (1969)	Hooded rat	FR 1; several nicotine doses and saline tested	Nicotine a reinforcer relative to saline	No quantitative data (from study abstract)
Yanagita (1977)	Rhesus monkey	Experiment 1: FR 1; several nicotine, caffeine, and saline doses substituted for SPA	Nicotine and caffeine not reinforcers, compared with saline or SPA	(preliminary report, Yanagita et al. (1974) studies)
		Experiment 2: FR 1; several nicotine doses continuously available	Nicotine S-A rates stable in most subjects, but not clearly dose related	No direct reinforcing efficacy test
		Experiment 3: PR procedures; two nicotine doses, saline, and three cocaine doses tested	0.2 mg/kg nicotine and lowest cocaine dose (0.03 mg/kg) maintained similar response rates, which slightly exceeded rates maintained by saline	Nicotine marginally reinforcing compared with saline and higher cocaine doses
Lang, Latiff, McQueen, Singer (1977)	Hooded rat	FR 1; nicotine and saline tested in food-sated and food-deprived rats	In food-deprived (not food-sated) rats, nicotine a reinforcer, compared with saline	
Singer, Simpson, Lang (1978)	Hooded rat	CONC [(FR 1:nicotine)FT 1 min:food pellet] in food-deprived rats; rats subsequently food-sated	Food satiation decreased nicotine S-A rate, but nicotine a reinforcer in both conditions	Results similar to ethanol testing results

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Griffiths, Brady, Bradford (1979)	Baboon	FR 160 followed by 3-hr timeout; several nicotine doses and saline substituted for cocaine	Number of nicotine injections/day did not exceed saline	Caffeine, ephedrine, and various other similarly tested stimulants were reinforcers relative to saline
Hansen, Ivester, Moreton (1979)	Albino rat	FR 1; several nicotine doses and saline tested	Mecamylamine (centrally acting antagonist), not pentolinium (peripherally acting antagonist), altered S-A behavior	Group data suggest nicotine as a reinforcer; no clear dose-effect curve
Latiff, Smith, Lang (1980)	Hooded rat	CONC [(FR 1:injection)(FT 1 min:food pellet)]; several nicotine doses and saline tested	Nicotine a reinforcer, relative to saline; mild effects of urine pH manipulations on S-A rate only during initial nicotine exposure	S-A rate inversely dose related during initial nicotine S-A behavior acquisition, not after establishment
Smith and Lang (1980)	Hooded rat	FR 1; one nicotine dose and saline tested	Nicotine a reinforcer with and without CONC food delivery schedule in food-deprived, but not food-sated, rats	
Goldberg, Spealman, Goldberg (1981)	Squirrel monkey	Second-order schedule FI 1 or 2 min (FR 10:stimulus), followed by 3-min timeout; one nicotine dose and saline tested	Nicotine maintained high rates of responding; rates decreased markedly when (1) saline replaced nicotine, (2) brief stimuli omitted, (3) subjects mecamylamine pretreated	Demonstrated importance of ancillary environmental stimuli in maintaining high rates of responding

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Dougherty, Miller, Todd, Kostenbauder (1981)	Rhesus monkey	FI 16 and second-order FI 1 min (FR 4:stimulus); several nicotine doses and saline tested	Nicotine maintained higher S-A rates than saline under FI and second-order schedules, but only a marginally effective reinforcer when continuously available	Establishing nicotine as reinforcer required several months, using procedures that establish cocaine or codeine as reinforcers in few days
Goldberg and Spealman (1982)	Squirrel monkey	FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested	Nicotine and cocaine qualitatively similar reinforcers, compared with saline; cocaine maintained higher rates of responding in 1 of 2 monkeys; mecamylamine pretreatment reduced nicotine S-A rates	Showed nicotine can be punisher, similar to electric shock
Singer, Wallace, Hall (1982)	Long-Evans rat	CONC [(FR 1:nicotine)(FT 1 min:food pellet)]; one nicotine dose tested	Lower nicotine S-A rates in rat group with 6-OHDA lesions in nucleus accumbens than in sham-lesions group	Range of lesion-inhibited scheduled-induced behaviors extended
Spealman and Goldberg (1982)	Squirrel monkey	Second-order FI 1, 2, or 5 min (FR 10:stimulus) and FI 5-min schedules tested; several nicotine and cocaine doses and saline tested	Nicotine and cocaine maintained similar rates of responding and patterns; nicotine, not cocaine, S-A decreased to saline-like rates when mecamylamine pretreated	Under both schedules, nicotine and cocaine reinforcing efficacy comparable

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Ator and Griffiths (1983)	Baboon	Experiment 1: FR 2 followed by 15-sec timeout; several nicotine doses, cocaine, and saline tested	Nicotine marginally reinforcing, compared with saline across narrow dose range	Inverted U-shaped initial dose-response curve; flat final curve (earlier abstract, Ator and Griffiths (1981))
		Experiment 2: FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested; FI duration varied 1-11 min	Nicotine maintained higher rates of responding than saline, but much lower than cocaine or food	Nicotine and injections/session responding rates little changed with varied FI duration
Goldberg and Henningfield (1983a, b)	Human and squirrel monkey	FR 10 followed by 1-min timeout; several nicotine doses and saline tested	Monkey and human patterns of responding qualitatively similar; nicotine injection number exceeded saline injection number in 3 of 4 of both humans and monkeys	In both humans and monkeys, evidence of nicotine having both reinforcing and punishing effects (from study abstracts)
Henningfield, Miyasato, Jasinski (1983)	Human	FR 10 followed by 1-min timeout; several nicotine doses and saline tested	Nicotine injection number generally exceeded saline injection number; nicotine injection number inversely related to nicotine dose; nicotine suppressed postsession cigarette smoking	Nicotine and intravenous cocaine subjective effects similar; nicotine had both reinforcing effects and punishing effects

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Risner and Goldberg (1983)	Beagle dog	FR 15 followed by 4-min timeout; several nicotine, cocaine, and saline doses tested; PR schedule also used	Nicotine and cocaine maintained qualitatively similar patterns of responding and were reinforcers relative to saline; mecamylamine pretreatment reduced nicotine, not cocaine, S-A	Substantially greater response rates maintained with cocaine than nicotine
Cox, Goldstein, Nelson (1984)	Wistar rat	FR 1; several nicotine doses and saline tested; a second inactive lever available to assess nonspecific activity-increasing nicotine effects	Nicotine S-A rates higher than saline, but result in part of nonspecific activity increases	Active lever responding rates low (+40 responses/12 hrs), only about twice as high as inactive lever rates
Prada and Goldberg (1985)	Squirrel monkey	FR 30 followed by 4-min or 10-sec timeout; one nicotine dose tested	At 4-min timeout, overall nicotine-maintained response rate range 0.3-2.4 responses/sec; at 10-sec timeout, responding poorly maintained	Nicotine iv injections and food pellet delivery maintained similar high response rates (from study abstract)
Slifer and Baister (1985)	Rhesus monkey	Experiment 1: FR 1 and CONC [(FR 1:nicotine)(FT 5-min:food pellet)]; several nicotine doses and saline tested Experiment 2: FR 10; saline and several nicotine doses substituted for cocaine	At CONC condition, nicotine S-A at rate higher than saline; at FR 1 condition, nicotine S-A without CONC food Nicotine a reinforcer relative to saline, but response rates low relative to single cocaine dose tested	At some doses, nicotine maintained higher S-A rates than at FR 1 condition saline (preliminary report, Slifer (1983)) Nicotine dose changes produced only small response rate changes

TABLE 4.—Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Goldberg and Henningfield (1986)	Human and squirrel monkey	Monkeys: FR 10-200, with 1-, 2-, or 4-min timeouts Humans: FR 10-800, with 1-, 5-, 10-, or 20-min timeouts	Nicotine maintained about 1.0/sec overall rate of FR responding at high FR and timeout, in both humans and monkeys	(from text of talk)
Naruse, Asami, Ikeda, Ohmura (1986)	Rat	FR 1, FR 4, FR 8; several nicotine doses and saline tested	Higher nicotine injection doses (10 and 30 µg/kg) maintained responding above saline control levels	Nicotine a relatively weak reinforcer after 15-day availability
De la Garza and Johanson (1987)	Rhesus monkeys	FR 10; saline and several nicotine, d-amphetamine, diazepam, and perphenazine doses substituted for cocaine	Nicotine a reinforcer relative to saline, but response rates very low relative to cocaine and d-amphetamine	Food deprivation significantly increased response rate for low nicotine dose in only 1 of 3 monkeys

NOTE: FR, Fixed ratio; SPA, 1-2 diphenyl-1-dimethyl-aminoethane-HCl; PR, progressive ratio; FT, fixed time; FI, fixed interval; CONC, concurrent.

peared to hasten acquisition of the nicotine self-administration (Smith and Lang 1980).

Since 1981, methodology for studying the reinforcing effects of nicotine has shifted away from continuous reinforcement schedules and toward schedules of self-administration in which responses are only intermittently reinforced by nicotine injection (Goldberg et al. 1983). Such intermittent schedules appear to more closely approximate the patterns of human cigarette smoking behavior in which nicotine is taken in intermittent small doses (puffs) and with even greater intervals between dosing resulting from periods of time between cigarettes (Henningfield 1984). On a variety of intermittent schedules, i.v. nicotine was shown to function as an effective reinforcer, maintaining overall rates of responding ranging from 0.1 to more than 1 response/sec (Table 4). These increases in behavioral responses maintained by nicotine were obtained without the use of food deprivation or concurrent inducing schedules of food delivery.

In one series of experiments with squirrel monkeys, Goldberg and Spealman (1982) and Spealman and Goldberg (1982) utilized a fixed-interval schedule in which the first response to occur after a 5-min interval elapsed produced an i.v. injection of nicotine followed by a 1-min period of drug nonavailability ("timeout"). Responses during the 5-min intervals had no specified consequences, and daily sessions ended after 10 intervals or 2 hr. Under these conditions, nicotine functioned as an effective reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.1 to 0.3 response/sec and were similar to those maintained by cocaine; (2) as nicotine dose per injection was increased from 3 to 300 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were about fourfold to eightfold higher than those maintained during saline substitution; and (4) daily intramuscular treatment with 1 mg/kg of mecamylamine reduced rates of responding maintained by nicotine to saline-control levels but had no effect on responding maintained by cocaine. Thus, nicotine satisfied all the criteria discussed in Chapter V as an effective reinforcer. Particularly striking was the finding that although injection doses of nicotine above 30 mg/kg produced vomiting during the session, one or more of these higher doses continued to be maintained near maximal rates of responding in four of the six monkeys studied.

The results of Goldberg, Spealman, and Goldberg (1981) showing nicotine to be an effective reinforcer have been extended in subsequent studies. For example, high rates of responding were maintained on reinforcement schedules of nicotine injection in which the number of responses per injection was fixed at some intermediate level (e.g., 1 injection/15 responses; such contingencies are termed fixed-ratio schedules). Risner and Goldberg (1983) used a 15-response fixed-ratio schedule of nicotine injection with 4-min

timeout periods following each injection in beagle dogs. Nicotine was an effective reinforcer in all dogs: (1) peak rates of responding were about 0.3 response/sec, but higher rates of responding were maintained by cocaine; (2) as the injection dose of nicotine increased from 10 to 100 mg/kg, response rates first increased and then decreased at the highest dose; (3) peak rates of responding maintained by nicotine were about fifteenfold greater than those maintained by saline; and (4) rates of responding maintained by nicotine but not by cocaine were reduced to saline levels by pre-session treatment with mecamylamine. Although cocaine maintained higher rates of responding than nicotine in the dog, fixed-ratio patterns of responding maintained by nicotine and cocaine were similar: a pause in responding at the start of each fixed ratio was followed by a change to steady responding at a high rate until nicotine or cocaine was injected.

In other studies Goldberg and Henningfield (1983a,b, 1986) used 10- to 30-response fixed-ratio schedules of i.v. nicotine injection in squirrel monkeys. When a 1-min timeout followed each injection, nicotine maintained rates of responding higher than did saline, although overall rates of responding were very low. When the timeout value was increased to 4 min (Prada and Goldberg 1985; Goldberg and Henningfield 1986) making maximum frequency of nicotine injection comparable to that of earlier studies by Goldberg and colleagues, nicotine maintained high rates of responding that ranged from 0.3 to 2.4 responses/sec in different monkeys.

Differences between nicotine and cocaine in their overall efficacy as intravenously delivered reinforcers have been found when the drugs are compared on progressive-ratio schedules. Risner and Goldberg (1983) studied beagles under a schedule in which the fixed-ratio requirement was increased daily until responding was no longer maintained. Cocaine maintained higher fixed-ratio values than did nicotine on this progressive-ratio schedule, although maximal fixed-ratio values for nicotine were well above those for saline. Yanagita (1977) obtained similar findings on a progressive-ratio schedule of i.v. nicotine or cocaine injection in rhesus monkeys (Chapter V).

Nicotine was also studied in the baboon using an intermittent schedule of reinforcement and was found to be a weak reinforcer. Ator and Griffiths (1983) used a 5-min fixed-interval schedule of i.v. nicotine injection in baboons with 1-min timeout periods. Peak rates of responding were higher than rates maintained during saline substitution. However, rates of responding maintained by nicotine were much lower than those maintained by i.v. injection of cocaine. In addition, as the injection dose of nicotine was increased from 10 to 560 mg/kg, rates of responding first increased and then decreased at the highest doses in one baboon. With the other two baboons, rates of responding either showed little change or decreased as injection dose

was increased. These variable dose-response data were consistent with the conclusion that nicotine was only a weak reinforcer in the baboons.

When cigarettes are smoked, a variety of environmental stimuli are intermittently associated with the pharmacologic actions of nicotine (e.g., pleasure and relief from withdrawal). These stimuli themselves appear important in controlling and strengthening repetitive cigarette smoking (e.g., removal of the sight and smell of cigarette smoking) (Gritz 1978). An experimental model for investigating the role of drug-associated stimuli is the second-order schedule of drug reinforcement. Second-order schedules of reinforcement involve the intermittent pairing or association of an environmental stimulus with the primary reinforcer; these stimuli are used as "secondary" or "conditioned" reinforcers to maintain chains of behavior leading eventually to the delivery of the primary reinforcer (Goldberg, Kelleher, Morse 1975; Katz and Goldberg, in press). These schedules add an additional component of relevance to the study of cigarette smoking: cigarette smoking involves the pairing of many such environmental stimuli (visual, olfactory, taste, and tactile) with the effects of nicotine administration.

Studies of i.v. nicotine on second-order schedules of reinforcement have shown that (1) nicotine can establish previously neutral stimuli (e.g., colored lights) as conditioned reinforcers when injections are paired with light presentations, (2) such schedules can result in high and persistent rates of drug-seeking behavior, and (3) the presentation of the stimuli themselves (in the absence of nicotine injections) could sustain substantial amounts of drug-seeking behavior. Goldberg, Spealman, and Goldberg (1981) and Spealman and Goldberg (1982) used a second-order schedule of nicotine injection in which completion of each 10-response fixed ratio during a 2-, 3-, or 5-min interval produced a brief visual stimulus; the first fixed ratio completed after the specified fixed interval elapsed produced both the visual stimulus and i.v. injection of drug. In these studies, nicotine functioned as a powerful reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.8 to 1.7 responses/sec and were similar to those maintained by cocaine; (2) as nicotine dose increased from 3 to 100 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were twofold to eightfold greater than those maintained during saline substitution; and (4) rates of responding maintained by nicotine, but not by cocaine, were reduced to saline control levels by pre-session administration of 1 mg/kg of mecamylamine; (5) the brief visual stimuli functioned as conditioned reinforcers, as demonstrated by the finding that rates of responding fell markedly when they were omitted during the intervals.

Taken together, the results of the studies described in this Section confirm that nicotine is self-administered in several animal species and in the absence of either tobacco or unique human cultural factors. It appears to be most effective as a reinforcer when intermittently available and when environmental stimuli are paired with nicotine delivery. Under these conditions, nicotine injections functioned to motivate behavior as did cocaine injections; however, cocaine injections maintained more total work output than did nicotine. Finally, studies with nicotine antagonists further confirmed that effects of nicotine in the brain were necessary to maintain its reinforcing actions.

Human Studies of Nicotine as a Reinforcer

The methods developed in animal studies have also been used to demonstrate the reinforcing effects of i.v. nicotine injections in human volunteers (Henningfield, Miyasato, Jasinski 1983; Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b, 1986). In these studies all subjects had histories of tobacco use and subjects were not allowed to smoke 1 hr before or during 3-hr sessions: During test sessions every 10th lever press produced an i.v. injection of either nicotine or saline followed by a 1-min timeout. In one study (Henningfield, Miyasato, Jasinski 1983), nicotine was available on some days, while saline was available on other days. In other studies (Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b), nicotine and saline were concurrently available for responding on alternate levers. With both approaches, all of the subjects initiated self-administration of nicotine. Nicotine injections were regularly spaced throughout each session, and the rate of self-administration was inversely related to dose. When saline was substituted for nicotine, rates of responding usually decreased; responding that did occur for saline occurred predominantly at the start of each session and was erratic in temporal patterns.

In another study, the fixed-ratio value was then increased to 100; following each injection, subjects then had to wait 20 min before another injection could be obtained (Swedberg, Henningfield, Goldberg, in press). Under these conditions rates of responding increased and ranged from 0.4 to 2 responses/sec, similar to those seen with squirrel monkeys and dogs in the studies previously described. These studies of i.v. nicotine self-administration demonstrated conclusively that nicotine itself can serve as an effective reinforcer in humans.

Nicotine as an Aversive Stimulus

Even dependence-producing drugs do not have invariant positive reinforcing effects; they may be aversive under some conditions (see Chapter V). Furthermore, aversive effects are an additional mechan-

ism by which drugs can modify behavior and may be important in gradually increasing the total amount of control which is exerted by the drug over the individual. Such effects of nicotine could be important in limiting the total amount of cigarette smoking or even in determining when the cigarette is discarded.

The potential effects of nicotine to produce severe discomfort and thereby limit further intake have been part of the history of nicotine which has developed over the centuries (Lewin 1931; Dixon and Lee 1912). Two types of laboratory studies have been conducted to assess possible aversive effects of nicotine. The studies, involving animals and/or humans, showed that nicotine (at high levels) can serve as a punisher to suppress behavior leading to the delivery of another reinforcer, and as an aversive stimulus or negative reinforcer to maintain behavior that either terminates or prevents injections of nicotine.

In one series of studies (Goldberg and Spealman 1982, 1983), squirrel monkeys responded on a two-component fixed-ratio schedule of food presentation. In both components, every 30th lever press produced a food pellet. In the punishment component, which was signaled by a red light, the first response in each fixed ratio produced an i.v. injection of nicotine. When responding produced 10- or 30-mg/kg injections of nicotine during the punishment component, responding was selectively suppressed in that component in a dose-related manner. When saline was injected, however, rates of responding for food were no longer suppressed. Similar findings were obtained when electric shock was compared with nicotine in the same studies. Administration of mecamylamine, but not hexamethonium, reduced the punishing effects of the nicotine, showing that the effects were centrally mediated. Furthermore, these antagonists did not reduce the aversive effects of the electric shock, confirming that the effects of nicotine were due to nicotine actions at nicotinic receptors and not to more general possible effects of nicotine.

The potential aversive effects of nicotine have been experimentally demonstrated in human subjects in a preliminary experiment by Henningfield and Goldberg (1983a). Human volunteers who had been recruited for studies of i.v. nicotine self-administration and who did not self-administer nicotine during initial sessions were tested under a concurrent schedule of nicotine avoidance and nicotine self-administration. Two levers were present, and injections of nicotine were programmed to occur every 15 or 30 min. Pressing the left lever 10 times avoided the impending injection, while pressing the right lever 10 times produced an injection. Higher doses of nicotine (1.5 to 4 mg/injection given over 10 sec) resulted in increased rates of pressing on the left lever, and fewer injections occurred. Subjects never completed the 10 responses on the alternate lever required to produce an injection. When saline was substituted for nicotine,

responding decreased and the number of injections received markedly increased. Analogously, in these same subjects scores on a visual line analog scale for rating "negative or undesirable" effects were directly related to nicotine dose, and declined to zero when saline was substituted for nicotine.

Nicotine as an Unconditioned Stimulus

The preceding studies have largely evaluated the effects of nicotine administration on some behavior which was associated with the drug by a specific behavioral contingency. But drugs can also directly elicit responses which then might become conditioned to occur in the presence of whatever stimuli were associated with those effects. The effects may be seen as positive or negative and may be associated with either increasing or declining drug levels in the body (i.e., drug taking or drug withdrawal).

Two general conditioning paradigms are used to evaluate the unconditioned stimulus effects of drugs and have been used to test nicotine: the conditioned place preference and aversion paradigm, and the conditioned taste aversion paradigm. In addition to a discussion of these paradigms, data obtained from the practical application of such findings in the treatment of tobacco dependence will be summarized.

Conditioned Place Preference and Aversion

The place preference and aversion paradigm has been increasingly used to evaluate the potential of drugs to produce dependence (Bozarth 1983). It may be used to assess the positive and negative subjective states induced by drugs and other chemicals. In the place-conditioning procedure, an animal is exposed to the effects of a drug in a novel, distinctive environment. Another environment is paired with the administration of the drug vehicle (e.g., saline). Subsequently, the subject is given a free choice of both environments while not under the influence of the drug. It is currently hypothesized that the formation of place preferences or place aversions depends on the association of the interoceptive drug effect with an external stimulus (e.g., the particular environmental context of the place-conditioning apparatus). Nicotine has been shown to condition both positive and negative effects in this paradigm.

The first published study of the place-conditioning effects of nicotine (Fudala, Teoh, Iwamoto 1985) indicated that nicotine, at doses from 0.1 to 1.2 mg/kg administered s.c. to rats, produced both a place preference and place aversion depending upon the dose. As discussed in Chapter V, the ability to condition both place preferences as well as place aversions is characteristic of several dependence-producing drugs. A dose of 0.8 mg/kg was found to condition a

place preference for previously nicotine-paired environmental cues in the greatest proportion of animals. At the lowest effective place-conditioning dose of nicotine, 0.1 mg/kg, an almost equal proportion of animals exhibited place preferences and place aversions. This investigation also indicated that mecamylamine, but not hexamethonium, blocked the place preference-producing effects of nicotine, suggesting that this nicotine-induced effect was centrally mediated.

Subsequent studies have extended the findings of Fudala, Teoh, and Iwamoto (1985) discussed above. Using a more conservative classification method in categorizing their subjects, Fudala and Iwamoto (1986) observed that nicotine produced a conditioned place preference only within the dose range previously tested. Furthermore, nicotine conditioned a place preference when the drug was administered immediately prior to conditioning sessions, but not when administered from 20 to 120 min prior to conditioning. Depending on the timing of nicotine administration, either place preferences or place aversions may be produced. For example, at doses between 0.2 and 0.8 mg/kg, a dose-dependent place aversion was induced when nicotine was administered 5 min or less following an animal's exposure to the conditioning environment (Fudala and Iwamoto 1987). One other group of investigators, Clarke and Fibiger (1987), using the same dose range of nicotine as in the two aforementioned studies, found no nicotine-induced conditioned place preference in rats. However, the two investigative groups used experimental methods that differed considerably, including differences in apparatus design, olfactory cues, number of conditioning trials performed, and time of conditioning relative to nicotine administration. The finding that nicotine administration can lead to conditioned responses in animals provides additional evidence of nicotine's potential to control behavior by this basic learning process (i.e., Pavlovian or classical conditioning, see Chapter V).

Conditioned Taste Aversion and Rapid Smoking

During conditioned taste aversion experiments, the presentation of an aversive stimulus after the consumption of a distinctively flavored solution causes rejection of the solution when it is presented at a later time (Palmerino, Rusiniak, Garcia 1980; Chapter V). A variety of dependence-producing drugs have been found to be effective at inducing taste aversions (for example, Wise, Yokel, DeWit 1976; Suzuki et al. 1983; Hunt and Amit 1987; Chapter V). Findings specific to nicotine are presented here.

Etscorn (1980) reported that a large intraperitoneal (i.p.) dose of nicotine, 2 mg/kg, conditioned taste aversions to 20 percent (weight per volume) sucrose in Swiss-Webster mice with the two-bottle choice test paradigm. Etscorn and colleagues (1986) also reported that i.p. injections of 1, 3, and 9 mg/kg of nicotine in golden Syrian hamsters

induced dose-related conditioned taste aversions to 0.1 percent sodium saccharin solutions with a single-bottle choice paradigm.

Kumar, Pratt, and Stolerman (1983) reported that s.c. injections of nicotine bitartrate could condition taste aversions to either 0.1 percent sodium saccharin or 0.9 percent sodium chloride solutions at doses as low as 0.08 mg/kg in Lister hooded rats with a two-bottle choice paradigm. The conditioned taste aversion was induced by nicotine in a dose-related manner; stronger taste aversions were induced by nicotine after four conditioning trials than after one or two trials. The S-nicotine (the nicotine form normally delivered in cigarette smoke) was approximately five times as potent as its stereoisomer in conditioning taste aversions. Mecamylamine, 0.1 to 2 mg/kg administered before each conditioning trial, blocked the development of taste aversions produced by 0.4 mg/kg of nicotine; hexamethonium, 1 to 10 mg/kg, had no effect.

Other studies have confirmed the pharmacologic specificity of nicotine-induced taste aversions; that is, Iwamoto and Williamson (1984) also found that the development of nicotine-conditioned taste aversions could be prevented in rats by pretreatment with mecamylamine, 3 mg/kg, but not with 1 mg/kg of hexamethonium. In an analogous study, the pharmacologic specificity of apomorphine- (dopamine agonist chemically derived from morphine) conditioned taste aversions was investigated in rats by establishing the response to both apomorphine and nicotine following pretreatment of the animals with pimozide (Kumar, Pratt, Stolerman 1983). Pimozide is a dopamine antagonist that blocks many of the effects of apomorphine. Pimozide pretreatment reduced the strength of the conditioned test aversions to apomorphine but not to nicotine, confirming a certain degree of pharmacologic specificity of the conditioning effects of these two chemicals. Finally, an intraventricular microinjection of 5 mg/kg of the quaternary nicotinic cholinergic ganglionic antagonist, chlorisondamine, in hooded Lister rats blocked the development of conditioned taste aversions to 0.1 percent sodium saccharin or 0.9 percent sodium chloride induced by nicotine injected 9 to 16 days after the chlorisondamine (Reavill et al. 1986).

These data indicate that nicotine, like some other drugs, is capable of conditioning taste aversions in a dose-related manner in rodents (see Chapter V). Because mecamylamine, but not hexamethonium, blocks nicotine-conditioned taste aversions, the mechanism by which nicotine conditions taste aversions appears to be centrally mediated. Conditioned taste aversion studies in which various combinations of nicotinic agonists and antagonists are given have also been useful in helping to identify specific brain mechanisms of nicotine's behavior modifying properties (see review by Stolerman, in press; also see Chapters III and V).

The fact that nicotine can be used to elicit aversive effects has been put to practical application in the treatment of cigarette smoking (Chapter V), generally to associate aversive effects of high doses of nicotine with the taste, smell, and inhalation of cigarette smoke. Variations on this procedure have been termed "rapid" smoking or "aversive" smoking procedures; the clinical results of these procedures have been mixed (see Chapter VII).

Nicotine: Withdrawal Reactions (Physical Dependence)

The preceding Sections have shown that cigarette smoking is an orderly form of drug self-administration. The role of nicotine in controlling this behavior is similar to the role of other psychoactive drugs in the determination of other forms of drug dependence (see Chapter V). Nicotine can serve as a highly effective positive reinforcer, and deprivation of cigarette smoking and presumably of nicotine itself can increase the reinforcing efficacy of cigarettes (Henningfield and Griffiths 1979). If longer periods of deprivation are associated with a discomforting withdrawal syndrome, this would constitute an additional mechanism by which the reinforcing efficacy of nicotine would be further increased. The drug effect which enables such discomforting withdrawal is physical dependence. Physical dependence refers to physiological and behavioral alterations that become increasingly manifest after repeated exposure to a pharmacologic agent. The primary indication of physical dependence is an abstinence-associated withdrawal syndrome, although tolerance is a frequent concomitant (Kalant 1978; Cochin 1970; Kalant, LeBlanc, Gibbons 1971; Eddy 1973; Clouet and Iwatsubo 1975; Yanagita 1977). Physical dependence and tolerance are discussed in greater detail in Chapter V.

Tolerance to nicotine has been studied since the 19th century and is well documented (Langley 1905; Dixon and Lee 1912; Gillman et al. 1985). As reviewed in Chapters II and V, nicotine produces tolerance to a variety of behavioral and physiological responses. Until the 1970s, however, physical dependence on tobacco was not rigorously studied, although there was evidence for a syndrome of withdrawal that could accompany abstinence from chronic cigarette smoking (Lewin 1931; Weybrew and Stark 1967) and that was significantly involved in attempts to quit smoking (Dorsey 1936). The clinical significance of the tobacco withdrawal syndrome has also been formally recognized by professional organizations such as the American Psychiatric Association (APA) (1980, 1987) and the American College of Physicians (1986). These observations, along with the evidence that nicotine produces tolerance (Chapter II), led to the conclusion that nicotine exposure produced physical depen-

dence (Jaffe 1985; Jaffe and Jarvik 1978; US DHHS 1986b; APA 1980).

Conclusions that nicotine exposure produced physical dependence were also consistent with early data which suggested that i.v. nicotine delivery seemed to relieve withdrawal from cigarettes and may have produced physical dependence in a nonsmoker (Johnston 1942). Other supporting observations included the finding that abrupt reduction of the nicotine in cigarettes (i.e., low nicotine-yield cigarettes) resulted in behavioral and physiological withdrawal signs including discomfort and the seeking of regular cigarettes (Finnegan, Larson, Haag 1945; Knapp, Bliss, Wells 1963). However, the rigorous scientific methods of the kind that were developed to evaluate withdrawal from opioids and sedatives (Himmelsbach 1942; Isbell 1948; Isbell et al. 1955; Chapter V) were not applied to the study of the tobacco withdrawal syndrome until the late 1970s. Therefore, the data available at the time of the 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health were not considered conclusive (US DHEW 1964). The present Section reviews characteristics of physical dependence on nicotine, including the relationship of nicotine intake to the magnitude of withdrawal signs and symptoms, and the role of both environmental and pharmacologic factors which influence the course of the withdrawal syndrome.

Criteria for Physical Dependence on Nicotine and Clinical Characteristics of the Withdrawal Syndrome

Similar kinds of phenomena characterize withdrawal syndromes from all drugs that produce physical dependence. If physical dependence on nicotine occurs, these same phenomena should be observed (see Chapter V; Martin 1977; Thompson and Unna 1977; Woods, Katz, Winger 1987). Based on these phenomena, criteria for establishing that physical dependence on nicotine occurs include the following: (1) Termination of cigarette smoking should be accompanied by changes in mood, behavior, and physical functioning. (2) Some of these changes should be in a direction which is opposite to those produced by cigarette smoking and should return to the baseline levels observed during chronic tobacco administration ("rebound effects"). (3) Physiological withdrawal effects should be reversible by nicotine administration.

The tobacco withdrawal syndrome as described by the APA in the revised Diagnostic and Statistical Manual (DSM III-R) (APA 1987), provides a clinical description (Table 5). Several of the symptoms of the nicotine withdrawal syndrome correspond to effects of nicotine that are either known or suspected to promote tobacco dependence as discussed in Chapter VI. It should be noted that the sequelae of tobacco abstinence include a range of responses which do not share the same underlying mechanisms. For example, some symptoms are

transient responses which are opposite those produced when nicotine is given and which subside within a few days or weeks of nicotine abstinence; such responses are presumed to reflect a physiological rebound occurring in the absence of chronic drug exposure. Other responses are also opposite those produced by nicotine administration but appear to primarily reflect the removal of nicotine exposure, and which may occur whether or not sufficient nicotine had been taken to produce physical dependence. An example of the latter type of response is body weight. Nicotine can directly suppress appetite and body weight, often below the value at which it would have been had nicotine not been taken; removal of nicotine is then accompanied by a stable increase in body weight.

Various lines of scientific evidence are available to characterize physical dependence on tobacco and to evaluate the specific role of nicotine. These data include surveys, treatment studies, and experimental laboratory studies and are briefly reviewed in this Section.

Retrospective Survey Data

Retrospective studies have been conducted with ex-smokers who were participating in major surveys (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987) or who were patients with chronic respiratory problems (Burns 1969; Mausner 1970). Other studies were conducted using subjects who responded to advertisements in newspapers (Pederson and Lefcoe 1976) or were contacted by word of mouth (Tahir 1967). The subjects in these studies had either quit smoking recently, had quit smoking for more than 1 year, or had at least one episode of remaining abstinent for 24 hr. Although the reliability of these data is limited because they are from retrospective self-reports, they provide information on the prevalence and nature of symptoms which may be experienced by smoke-deprived persons and acutely abstinent smokers.

Symptoms reported by significant numbers of ex-smokers included: "craving" for tobacco (Hughes, Gust, Pechacek 1987; Tahir 1967; Burns 1969; Mausner 1970; Pederson and Lefcoe 1976); restlessness, nervousness, or irritability (Tahir 1967; Wynder, Kaufman, Lesser 1967; Burns 1969; Mausner 1970; Hughes, Gust, Pechacek 1987); anxiety (Hughes, Gust, Pechacek 1987); impatience (Hughes, Gust, Pechacek 1987); difficulty concentrating (Tahir 1967; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); somatic or physical complaints (Hughes, Gust, Pechacek 1987; Pederson and Lefcoe 1976); increased appetite (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); increased food intake (Wynder, Kaufman, Lesser 1967); and weight gain (Tahir 1967; Wynder, Kaufman, Lesser 1967; Mausner 1970; Pederson and Lefcoe 1976).

Measures of the incidence and magnitude of signs and symptoms vary across studies, at least partly because of the diversity of the

TABLE 5.—Diagnostic categorization and criteria for nicotine withdrawal

Nicotine-induced organic mental disorder	
292.00 Nicotine Withdrawal	<p>The essential feature of this disorder is a characteristic withdrawal syndrome due to the abrupt cessation of or reduction in the use of nicotine-containing substances (e.g., cigarettes, cigars, and pipes, chewing tobacco, or nicotine gum) that has been at least moderate in duration and amount. The syndrome includes craving for nicotine; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain.</p> <p>In many heavy cigarette smokers, changes in mood and performance that are related to withdrawal can be detected within 2 hours after the last tobacco use. The sense of craving appears to reach a peak within the first 24 hours after cessation of tobacco use, and gradually declines thereafter over a few days to several weeks. In any given case it is difficult to distinguish a withdrawal effect from the emergence of psychological traits that were suppressed, controlled, or altered by the effects of nicotine or from a behavioral reaction (e.g., frustration) to the loss of a reinforcer.</p> <p>Mild symptoms of withdrawal may occur after switching to low tar/nicotine cigarettes and after stopping the use of smokeless (chewing) tobacco or nicotine gum.</p> <p>The diagnosis of Nicotine Withdrawal is usually self-evident from the person's history, and disappearance of the symptoms if smoking is resumed is confirmatory. However, withdrawal from other psychoactive substances may take place simultaneously, and produce similar symptoms.</p> <p>Diagnostic Criteria for Nicotine Withdrawal</p> <p>A. Daily use of nicotine for at least several weeks</p> <p>B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by at least four of the following signs:</p> <ol style="list-style-type: none"> (1) Craving for nicotine (2) Irritability, frustration, or anger (3) Anxiety (4) Difficulty concentrating (5) Restlessness (6) Decreased heart rate (7) Increased appetite or weight gain

SOURCE: Condensed from the American Psychiatric Association (1987).

measuring instruments and techniques used, questions asked, and populations examined. Collectively, the results of many such studies suggest that most nicotine-deprived cigarette smokers experience at least one symptom of the tobacco withdrawal syndrome, that between one-fourth and one-half show significant withdrawal, and that about one-fourth report no withdrawal at all (Pederson and Lefcoe 1976; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987; Gritz 1980; Henningfield 1984). Of those persons who retrospectively report experiencing no withdrawal symptoms, it is unclear whether they were not physically dependent, whether the assessment instruments were not sufficiently sensitive, or whether